REMARKS

Priority

The Examiner has acknowledged priority of claims 18-34 of the instant application to U.S. Provisional Patent Application Serial No. 60/602,817 filed August 18, 2004. The Examiner, however, stated that one or more claims of the subject application are not supported or enabled in the manner provided by the first paragraph of 35 USC §112 by the disclosure of prior-filed application, Application No. 60/535,496. The Examiner stated that the disclosure of Application No. 60/535,496 fails to provide adequate support for the instantly claimed step of administering "(b) one or more immunotherapeutic agents" in addition to administering an antisense oligonucleotide.

Applicants respectfully disagree with the Examiner for the following reasons. Priority Application No. 60/535,496 describes combinations of an antisense oligonucleotide against ribonucleotide reductase R2 with various known anticancer therapeutics, including cytokines (such as interferons and interleukins), for the treatment of cancer (see, for example, page 15, lines 9 to 11). Priority Application No. 60/535,496 further describes specific applications of such combinations in the treatment of cancer, for example, a "combination of the antisense oligonucleotide and a cytokine (for example an interferon or an interleukin) may be used in the treatment of renal carcinoma, for example early stage renal carcinoma" (see page 16, lines 9 to 10), and "a combination of the antisense oligonucleotide and one or more cytokines for the treatment of renal cancer, or breast cancer, AML, lung cancer (NSLC OR SCLC), prostate or colon cancer, or a variety of solid tumours" (see page 16, lines 3 to 5).

As would be readily understood by a worker skilled in the art, in light of common general knowledge, cytokines are a representative sub-class of the more general class of "immunotherapeutic agents," as described in the present application (see, for example, the definition at page 9, lines 1 to 6). Accordingly, Applicants assert that the description in priority Application No. 60/535,496 of the combination of an antisense oligonucleotide against ribonucleotide reductase R2 and a cytokine supports claims to combination therapy comprising administering "one or more immunotherapeutic agents" in addition to an antisense oligonucleotide against ribonucleotide reductase R2, as recited in the presently pending claims.

In this regard, Applicants also respectfully refer the Examiner to the USPTO Manual of Patent Examining Procedure (MPEP) Section 2163.04, which states "The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97." The Applicants respectfully submit that the Examiner has not met this burden.

Applicants further assert that priority Application No. 60/535,496 provides extensive teaching with respect to testing the efficacy of the combinations in inhibiting tumor growth and treating cancer (see page 23, line 20 to page 30, line 16, and the Examples) and note that when the application was filed, immunotherapy was a well-established art and the levels of skill and knowledge in the art were high. Accordingly, Applicants assert that the worker skilled in this highly developed art, in light of the guidance provided by the specification of priority Application No. 60/535,496, could have readily made and used the invention as presently claimed and would have concluded that Applicants were in possession of the claimed invention at the time priority Application No. 60/535,496 was filed.

Accordingly, Applicants submit that the disclosure of priority application, Application No. 60/602,817, provides adequate support and enablement in the manner provided by the first paragraph of 35 USC §112 for the claims of the instant application and, therefore, that the claims should be afforded a priority date of January 12, 2004 (the filing date of priority application, Application No. 60/602,817).

Claim Objections

The Examiner rejected claim 21 for containing non-elected subject matter. In order to advance prosecution of the instant application, please withdraw claim 21. We believe this will render the Examiner's objection moot in this regard.

Claim Rejection under 35 USC §102 – Anticipation

The Examiner rejected claims 18-20, 23, 25, 28-29 and 33-34, under 35 USC §102(b) as being anticipated by Wright *et al.*, in WO 98/00532 (hereinafter referred to as "Wright-A"). The Examiner states that Wright-A teaches a method of treating a metastatic cancer or a solid cancer in a mammal comprising administering a pharmaceutical composition comprising 1) a phosphorothioate-modified antisense

oligonucleotide that is at least 7 consecutive nucleotides complementary to SEQ ID NO:43, which is 39 nucleotides in length and is complementary to nucleotides 2007-2045 of SEQ ID NO:105 of the instant application and 2) specific antibodies such as monoclonal antibodies, wherein the mammal is a human (referring to pages 7, 11, 13-16 and claims 7, 8, 10-13, 26-30). The Examiner alleged, therefore, that all the claim limitations are taught by Wright-A.

Applicants respectfully traverse the Examiner's rejection for the following reasons. Wright-A describes oligonucleotides which comprise an untranslated region (UTR) from a housekeeping gene and their ability to modulate cell growth and differentiation. Wright-A describes that an antisense sequence, which preferably comprises a sequence complementary to the entire UTR, may be used to inhibit or enhance the effect of these oligonucleotides (see, page 9, lines 10-13). With respect to antibodies, Wright-A describes that the oligonucleotides described therein may be used to prepare antibodies (see, page 10, line 24). Wright-A also describes the use of such antibodies to detect and quantify UTRs in a sample (see, page 12, lines 4 to 9). Wright-A further describes, as an alternative to the use of an oligonucleotide, ribozyme or antisense, use of such an antibody to modulate cell growth (see, for example, page 14, lines 36 to 38). With respect to combinations, Wright-A teaches pharmaceutical compositions comprising, and methods of modulating tumorigenicity of neoplastic cells using, one or more oligonucleotides, ribozymes, or antisense oligonucleotides (see claims 10 to 13, and 26 to 30, as cited by the Examiner). Wright-A does not, however, describe combining an antisense oligonucleotide with an antibody as alleged by the Examiner.

In contrast to the teaching of Wright-A, pending claims 18-20, 23, 25, 28-29 and 33-34 relate to antisense oligonucleotides against ribonucleotide reductase R2 in the treatment of cancer when used in combination with a specific type of anticancer agent: an immunotherapeutic agent, which, as demonstrated in the present application, shows an improved efficacy over the use of the antisense oligonucleotides alone (see Examples provided in present application). Accordingly, Applicants assert that Wright-A does not teach all the claim limitations of pending claims 18-20, 23, 25, 28-29 and 33-34 and that these claims thus are not anticipated by Wright-A. Applicants, therefore, respectfully request that the Examiner withdraw this rejection.

Claim Rejection - 35 USC §103 – Obviousness

The Examiner rejected claims 18-34 under USC § 103 (a) as being unpatentable over Lee *et al.* (*Cancer Research,* 2003, 63:2802-2811, citation of record, also applicant's citation) (hereinafter referred to as "Lee") in view of Hatanaka *et al.* (*The Journal of Gene Medicine*, 2004, 6:1139-1148) (hereinafter referred to as "Hatanaka").

Specifically, the Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the antisense anti-cancer agent of "GTI-2040" of Lee in the method of combination cancer therapy of Hatanaka. The Examiner further alleged that one of ordinary skill in the art would have been motivated to treat cancer in a cancer patient by administering "GTI-2040" of Lee together with a cytokine IFN-α so as to achieve a synergistic anti-cancer therapeutic effect for treating advanced, metastatic cancer because Hatanaka taught that antisense and IFN-α combination therapy results in significant synergistic cancer growth inhibition effect in a mammal, and because the antisense agent "GTI-2040" of Lee was an art-recognized anti-cancer therapeutic agent tested in human patients. The Examiner furthermore alleged that one of ordinary skill in the art would have been motivated to enhance the anti-cancer efficacy of "GTI-2040" by virtue of increasing immune stimulation, which the Examiner

alleges is one of the inherent properties of "GTI-2040" described by Lee, by adding an immune stimulatory agent, for example IFN-α, because the Examiner alleges Lee taught that overall anti-cancer effect of "GTI-2040" was partially achieved by its inherent immune stimulatory property.

Applicants respectfully traverse the Examiner's rejection for the following reasons. Firstly, Lee et al. is not prior art under § 102(a) because it is not a publication by another as stated in the statute. Applicants submit herewith a declaration under 37 C.F.R. § 1.131 stating the experiments described in Lee et al. that relate to the invention were the joint contributions of the instant inventors, notwithstanding the inclusion of additional authors on the publication. Because Lee et al. was not published more than one year prior to the priority date of this application, it does not qualify as prior art under § 102(a) and, therefore, this rejection should be withdrawn.

Secondly, with respect to Hatanaka, Applicants submit that Hatanaka also is not prior art under 35 USC §102(a). The earliest publication date of Hatanaka (first published online on September 28, 2004 per http://www3.interscience.wiley.com/journal/109659044/abstract; copy attached herewith) is after both the priority dates of January 12, 2004 and August 18, 2004 for the instant application. Accordingly, Applicants submit that Hatanaka does not qualify as prior art under 35 USC §102(a). As such, Applicants believe that the Examiner's allegations with respect to Hatanaka in combination with Lee are rendered moot and, therefore, this rejection may be withdrawn.

The Examiner rejected claims 18-34 under USC §103(a) as being unpatentable over Wright *et al.* (US 5,998,383) (hereinafter referred to as "Wright-B") in view of Pavlick *et al.* (*Expert Opinion on Investigation Drugs,* 2003, 12:1546-1558) (hereinafter referred to as "Pavlick").

The Examiner stated that Wright-B teaches a combination cancer treatment method in a mammal comprising administering a therapeutic drug and an antisense

oligonucleotide of SEQ ID NO:42, which is identical to SEQ ID NO:1 of the instant application, wherein the cancer treatment method inhibits cell growth and metastasis of tumor cells in a human patient. The Examiner further stated that Wright teaches that the combination treatment method can be used to treat various forms of cancer including a metastatic cancer and a solid cancer and that antisense oligonucleotide comprises phosphorothioate linkages for increased nuclease resistance (referring to columns 6-12; Table 7, claims 11-13, 18-20, 30-31). The Examiner stated that Wright-B does not teach a combination therapy further comprising immunotherapeutic agents.

The Examiner stated that Pavlick teaches that one of the first combination therapies in the art is concurrent "biochemotherapy" clinical trials comprising immunotherapy (e.g., administering non-specific cancer vaccines, specific cancer vaccines, cytokine-adjuvants, antibodies or cytokines) combined with conventional chemotherapy (e.g., administering cisplatin, vinblastine, or dacarbazine). The Examiner further stated that Pavlick discusses that combination therapeutic strategies further comprising a target-specific antisense oligonucleotide agent are also promising because of the low toxicity and low side-effect profiles of antisense oligonucleotide agent.

The Examiner alleged, therefore, that it would have been obvious to one of ordinary skill in the art at the time the invention was made to devise a first-line systemic combination cancer therapeutic strategy of administering the antisense anti-cancer agent of SEQ ID NO:42 of Wright-B and immunotherapeutic agents, further comprising chemotherapeutic agents. The Examiner further alleged that one of ordinary skill in the art would have been motivated to do so in order to increase the therapeutic efficacy of a single anti-cancer agent-based therapy (e.g., antisense alone, chemotherapy alone, immunotherapy alone) for treating advanced, malignant, and metastatic cancer, because of the problem and inadequacy of single anti-cancer agent-based therapy for treating such advanced, malignant, and metastatic cancer were recognized in the art and a new cancer treatment design was thus needed in the art, and because only a finite number of

identified, predictable potential solutions (e.g., antisense agent combined with chemotherapy, immunotherapy combined with chemotherapy, antisense agent combined with any cancer therapeutic strategies) were recognized in the art as taught by Wright-B and Pavlick.

The Examiner further alleged that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention and that the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing since the clinical efficacy and safety of the antisense agent of Wright-B (identical to the instantly claimed antisense agent of SEQ ID NO:1) were known in the art of cancer treatment, and since one of ordinary skill in the art would have had good reason to pursue one of the known options of combination cancer treatment methods for enhanced therapeutic outcomes, wherein one of the options is the combination comprising immunotherapy and antisense agent as first-line systemic therapy, further comprising chemotherapy, and since such combination cancer therapeutic strategy was within the technical grasp of the ordinary skilled artisan at the time of the invention, as evidenced by the state of the art and technology described by Wright-B and Pavlick.

Applicants respectfully traverse the Examiner's rejection for the following reasons. With respect to Wright-B, this reference describes combination therapy of antisense oligonucleotide with chemotherapeutic drugs. With respect to Pavlick, this reference is concerned with various investigative therapies being explored to manage malignant melanoma. As such, Pavlick discusses the potential application of novel treatment agents such as vaccines, monoclonal antibodies, antisense therapy, antiangiogenetic agents and small molecules targeted to interrupt intracellular signalling pathways. Pavlick describes the inadequacy of most single-agent chemotherapies in metastatic melanomas and the potential of combination chemotherapy is considered. As noted by the Examiner, this reference also discusses "biochemotherapy," in particular sequential administration of a chemotherapeutic drug followed by IL-2 and/or IFN (see Table 3). Pavlick discusses that

while the addition of immunological adjuvants to chemotherapeutic regimens has been associated with overall response rates of between 35%-45% in patients with metastatic melanoma, this was at a cost of significant toxicity to patients and no significant improvement in survival rates (see abstract and Table 3). More recent clinical trials reported in Pavlick had showed no significant difference between groups treated with chemotherapy alone and groups treated concurrently with chemotherapy and IL-2 and IFN (see page 1555, column 1, first paragraph). As such, Pavlick teaches that the success of such biochemotherapies was still uncertain. Pavlick also includes a general comment referencing that IL-2 is currently being tested in conjunction with other cytokines and immunotherapies (page 1549, column 2, lines 31-33).

With respect to antisense therapy, Pavlick generally describes the concept of antisense therapy at page 1551 (column 1, seventh paragraph) and more specifically discusses clinical trials relating to the use of a BCL-2 targeted antisense oligonucleotide and a standard chemotherapeutic, dacarbazine, in Stage IV melanoma patients (see page 1551, column 2, second paragraph). Pavlick also speculates on the possibility of combining BCL-2 antisense with an enzyme inhibitor as the first step in a specific type of treatment program. As a second step in this program, Pavlick proposes a separate maintenance regimen employing "immunologically active vaccines." Pavlick postulates that this may provide an attractive regimen, but acknowledges it will require further investigation (see page 1555, paragraph bridging columns 1 and 2).

Pavlick does not, however, even speculate on combining administration of an antisense oligonucleotide with administration of an immunotherapeutic, such as a cytokine, for the treatment of malignant melanoma, and thus Pavlick, alone or in combination with Wright-B, fails to suggest methods of treating cancer with a combination of an antisense oligonucleotide with an immunotherapeutic as recited in the pending claims. Moreover, given the uncertainty of the outcome of the combination therapies described in Pavlick, the skilled worker having reference to Pavlick would not

have a reasonable expectation that the various combinations speculated upon would be successful in improving the effect of either component alone in treating melanoma. In contrast, the present application demonstrates that the combination of an antisense oligonucleotide targeted to ribonucleotide reductase R2 and an immunotherapeutic results in an improved inhibition of cancer growth for various cancers when compared to treatment with either agent alone (see, for example, Examples 2 to 7 and Figures 2 to 7 of the instant application).

For the reasons set forth above, Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the subject matter of pending claims 18-34 in view of the combination of Wright-B and Pavlick. Applicants assert that combination of Wright-B in view of Pavlick fails to render the subject matter of pending claims 18-34 obvious and, therefore, that pending claims 18-34 submitted herewith comply with 35 USC §103(a). Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for two months, to and including September 2, 2009, and a check in payment of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 2, 2009

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